Transport in the Preterm Infant Brain: Quantitative Analysis of the Relative Roles of Pulsatile Flow and Diffusion

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Introduction

The transport of nutrients and neurochemicals to developing brain white matter (WM) cells involves several processes. First, the delivery of nutrients and other molecules to the capillaries occurs via cerebral blood flow (CBF), followed by the secretion of an ultrafiltrate of the blood plasma and transcellular fluid through the tight junctions between the vascular endothelial cells. At the same time, cerebrospinal fluid (CSF) – which includes vitamins, nucleosides, purines, glucose, amino acids, some proteins, leukocytes and, from clearance from injury, toxic metabolites, cellular debris and edema - also communicates with the extracellular fluid (ECF). Next, the ECF experiences a pulsatile flow through the WM cell matrix, providing convective flow-based transport. Accompanying this is the diffusion of molecules in the ECF. These processes combine to form the WM ECF environment and present molecules, ions and water to the cell surface and surface molecules of developing brain WM cells in the preterm infant brain. Little previously was known regarding the relative amounts of new ECF and its constituents that enter voxels due either to flow or diffusion individually, since available ADC values from DT-MRI include ECF flow as a contribution to the diffusion measurements. In (1) we described a frequency band-specific pulsatile flow imaging approach to analyze pulsatile flow, based on a rapidly acquired gradient-recalled EPI times series in a select imaged slice. The time dependent signal from each voxel in the time series of EPI images reveals an initial signal decay due to the repeated excitation of the same anatomy and an asymptotic steady-state signal, both functions of the inflow from out-of-slice fresh nuclear spins. The steady-state signal and the initial decay slope are individually dependent linearly (to a first approx) on the local average proton density, while (-1x) their ratio is (to a first approx) independent of proton density and has units of time. We denote this ratio as a flow and diffusion-related time constant, Ts. By modeling relative amounts of ECF+CBF inflow plus diffusion, we can compare to voxel-specific time dependent signals from the preterm infants studied to determine the volume percent of new spins in fluid entering each voxel per unit time. The approximate contribution of diffusion to each voxel's characteristic time dependence can be modeled using preterm infant specific ADC values (2), then volume percents can be computed of ECF+CBF flow and, separately, diffusion.

Methods

30 (18 M; 12 F) preterm infants (both neurologically normal infants and infants exhibiting brain pathology) underwent MRI examinations at 28-43 weeks postconceptional age. Institutional approval for MRI was obtained, and in each case informed consent of both parents was obtained. All infants fed prior to and slept during the exam.; no sedation was used. There was constant supervision by a physician. ECG and O2SAT monitoring and hearing protection were used, and a vacuum fixation pillow cradled the head and body. Data were acquired on a 1.5T GE HORIZON LX Echospeed MR Scanner using a commercial head coil. Morphological MRI and volumetric linescan DT-MRI (3) were initially obtained. Flow imaging raw data were obtained in each case from an axial brain slice superior to the lateral ventricles with Nyquist frequency 6.0Hz using gradient-recalled echo planar imaging with: TE 45ms TR 167ms, FA 45deg, 64x64 matrix, FOV 15cm, 1 NEX, 256 sequential acquisitions, 3.0mm thick, Bw 62.5kHz, ν=A/P, 1/2 phase encoding. A brain mask was created for each subject from steady-state data and eroded four times to eliminate CSF dominated intracranial space. For each voxel in the mask, the ratio of the steady-state signal and (-1x) the initial signal decay slope was computed, and the median value over the mask was recorded. A three compartment model of the voxel magnetization and pulse sequence was developed and programmed in Matlab. Compartments included intra-voxel space inaccessible (1; approx 80%) or accessible (2; approx 20%) to spins entering from flow and diffusion and, (3) space external to the voxel modeled where previously excited spins can be transported to, but experience no further RF excitation. Published infant brain T2* values (4) and T1 values (5) were used. Diffusion modeling assumed diffusion into an infinite slab integrating erfc(x/2*sqrt(Dt)), using the maximum ADC value we observed (2) in 28wk PCA preterm infants (ADC 1.8x10-3 mm^2/sec).

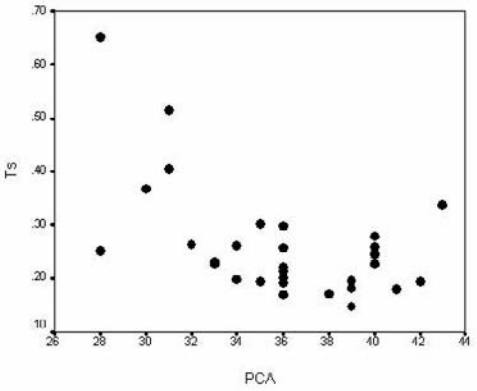

Fig.1 Signal Decay Time Constant, Ts, (median of whole brain results) versus preterm infant age (wks PCA)

Results

Experimental results of Ts are shown in Fig.1. Simulation results reveal three possible fundamental explanations for the age variation in Ts: (Case 1) the fraction of flow+diffusion can be fixed and T2* changes alone within a voxel can describe the change; (Case 2) T2* can be relatively constant, and changes in the fraction of flow+diffusion can produce the change; and, (Case 3) a combination of changes in flow fraction and T2* occur with age. Comparing experimental results to simulation, the volume percent of flow+diffusion providing new spins is 18-22%. Diffusion modeling results show that $\leq$4% of new spins could enter due to diffusion in the maximal case. Separating by subtraction shows that flow (ECF and CBF) can provide 14-18% of the new spins to a voxel per unit time, while diffusion provides $\leq$4%.

Conclusion

Combined results of experiments and simulations show that pulsatile flow can account for approx 4x more inflow into WM tissue compared to the contribution of diffusion. This is the first quantitative separation of flow and diffusion in the preterm brain. Understanding these processes is key to elucidating changes in extracellular flow within the brain that may related to local changes in tissue properties that may relate to changes in transmembrane transport, diffusion and potentially affect drug delivery within the brain.

References

(1) GP Zientara, LP Panych, JS Soul, JJ Volpe, FA Jolesz, Abs 9th ISMRM, 2001, 406. (2) PSHuppi, S .Maier, S Peled, GP Zientara, PD Barnes, FA Jolesz, JJ Volpe, Pediatric Research, 44:584-590 (1998). (3) SE Maier, Magn Reson Med, 2001, 46(6):1136-1143. (4) MJ Rivkin, et al, Magn Res Med 51(6):1287-91 (2004). (5) RG Steen, et al Am J Neuroradiol 18:819-828 (1997).

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